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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/007,078	11/08/2001	Donna T. Ward	RTS-0236	6940

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	9

DATE MAILED: 02/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE

Office Action Summary	Application No.	Applicant(s)	
	10/007,078	WARD ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2002 and 03 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15,20-24,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15,20-24,26 and 27* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicants' response to the Office action mailed May 7, 2002 has been entered and as per its instructions, claims 16-19 canceled, 15 and 20 amended, and 21-17 added. Applicants' response to the restriction requirement mailed November 1, 2002 has been entered and as per its instructions, claim 25 canceled. Applicants' arguments regarding the restriction requirement have been noted, but are moot in light of the cancellation of claim 25.

Applicant's responses have been considered. Rejections and/or objections not reiterated from the previous office action mailed May 7, 2002 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Response to Arguments

2. Claim 20 stands rejected, and added claims 21-24, 26 and 27 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of EIF2C1 expression in vitro, does not reasonably provide enablement for *in vivo* antisense-mediated modulation of an endogenous RNA-mediated interference pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant traverses the enablement rejection of the Office action mailed May 7, 2002 by asserting that the previously cited references do not actually support the examiner's conclusion that the application of antisense *in vivo* is highly unpredictable. Applicants argue that when read as a whole, the papers cited teach the potential usefulness of antisense drugs in humans, and further, don't provide a reasonable basis to doubt that the antisense activity seen in *in vitro* cell cultures would also occur in cells in the *in vivo* whole animal and humans.

Applicants response of the above rejection primarily focuses on the reference of Crooke et al., wherein Applicant argues that it is a fundamental principle of drug development that data from whole cell studies are directly applicable to *in vivo* activity, and that Crooke provides no reason to doubt this. Applicants point to a passage from Crooke et al. that indicates the successful use of oligonucleotides in *in vitro* studies, and finally conclude that "Nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*". Applicants arguments regarding the remaining references center on the assertion that nowhere is it indicated that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

These arguments are not adopted. At the outset it is acknowledged Applicants' quotation of Crooke et al. is indicative of the state of the art; "....numerous well-controlled studies have been reported in which antisense activity was conclusively demonstrated [*in vitro*]." Indeed, antisense inhibition is routinely performed by those of skill in the art *in vitro,* and the previous Office action granted that such inhibition is enabled by the present specification; it is the

extrapolation of this *in vitro* demonstration of antisense inhibition to the *in vivo* whole animal that is the subject of the present enablement rejection.

Contrary to Applicants argument that none of the referenced citations indicate that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable, the reference of Crooke et al. does indicate a high level of unpredictability in critical elements of antisense-mediated gene inhibition. Applicants are directed to page 3, first paragraph: "Finally, extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man that demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies..." According to the reasoning in this passage, it follows that any oligo which is taken up by a cell *in vitro*, even if it proceeds to inhibit the target, that no meaningful prediction can be made as to whether the oligo will ever be taken up by cells *in vivo*; such uptake *in vivo* is required for subsequent target inhibition as understood by one of skill in the art. Accordingly, this passage contradicts Applicants assertions that nowhere in the reference does the author state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity *in vivo*. Because Applicants provide no other evidence or passages that support their assertion that Crooke et al. does not indicate unpredictability, Applicants' arguments regarding the reference of Crooke et al. are not convincing.

Applicants further assert that the fundamental principle of drug development is to progress logically from activity in cells to activity in humans, and that Crooke et al. does not provide any reason to doubt that this fundamental principle is applicable to antisense agents. While Applicants broad theory of drug development has been widely used in the discovery of small organic molecule inhibitors, this generalization ignores the very specific art-recognized problems peculiar to the development of antisense drugs that were discussed in the previous Office action. Chief among these issues are cellular uptake of oligos, inhibition of oligo hybridization to the target by RNA secondary structures and translation complexes, maladaptive immune responses to the administered oligo, and non-specific oligo binding to endogenous proteins. Applicants arguments have not addressed these art-recognized barriers to antisense drug development aside from the above-listed assertions. No additional evidence or literature has been presented beyond Applicants statements that nowhere in the cited references is it indicated that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable.

In regards to Applicants statements that nowhere in the remaining articles is it found that extrapolation from *in vitro* data on antisense compounds to *in vivo* effects is unpredictable, the examiner disagrees with this position. While the articles present the challenges inherent in attaining *in vitro* experimental success, the stated eventual goal of all of these articles is the application of antisense-mediated inhibition *in vivo*; this theme underlies all the literature cited in the previous Office action. For example, in Branch et al. on page 49, far right column, line 25-30, the subject of unpredictability is broached; "With so many possible sequences to choose from, and the likelihood that *in vitro* studies will not always predict *in vivo* efficacy,

straightforward new screening techniques need to be developed for use in cells." Gewirtz et al. indicate (at page 3162, center column, 2nd to last paragraph) that studies of a transfection agent GS2888 complexed with antisense oligos have been successful in cell culture, but studies in primary cell lines are needed. Gewirtz adds that "while the application of GS2888 [a transfection agent] to cell culture experiments has been clearly demonstrated, its utility for therapeutic applications remains to be determined." Agrawal et al. (attached herewith) devotes the closing section on the unpredictabilities of *in vivo* efficacy, how moving from cell culture to the *in vivo* whole animal is an important hurdle where no reasonable degree of success can be assured. These passages all imply or explicitly state difficulty in attaining therapeutic success, and underscore how such success has been so elusive. That the articles don't focus on *in vivo* efficacy appears to be a function of its unpredictability; there simply is not much to say on the subject, because there is so little success to discuss.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, and 4-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Koesters et al., in view of Taylor et al., Baracchini et al., and Milner et al.

Applicants traverse the rejection of the prior Office action. Applicants' traversal is based on the argument that the sequence of Koesters et al., referenced at GenBank accession number AF093097, which comprised the primary reference of the instant rejection, is not the same as the

instantly claimed SEQ ID NO: 3, which is referenced at GenBank accession number NM_012199.1. Applicants argue that the reference of Taylor et al., which was relied upon to teach that antisense can be designed to inhibit any gene whose sequence is known, does not state that such antisense are expected to inhibit expression., and that it is only with testing of compounds that one can know if antisense compounds are capable of inhibiting gene expression. Finally, Applicants also argue that the remaining references do not cure the deficiencies of the references described above, and that none teach or suggest antisense compounds of any type targeted to EIF2C1 nucleic acid molecules as claimed.

Applicant's arguments have been fully considered but they are not persuasive. Upon comparison of the sequence contained at GenBank accession number AF093097 with that of the instantly claimed SEQ ID NO: 3, and referenced at GenBank accession number NM_012199.1, the polynucleotides are identical, both in length and sequence (see enclosed sequences).

Furthermore, Applicants' arguments that Taylor et al. teach how to make antisense sequences but does not teach whether each individual sequence will work is not adopted. This line of reasoning basically alleges that Taylor et al. does not provide an enabling disclosure of how to make and use antisense molecules targeted to a sequence; however, Applicants have provided no evidence that the sequences taught by Taylor et al. would fail to inhibit gene expression. Moreover, there are many successful demonstrations in the prior art of antisense-mediated gene inhibition *in vitro*, as can be seen in the references supporting the enablement rejection of the last Office action. In the absence of convincing evidence that Taylor et al. is not enabled, the instant rejection of the previous Office action is considered appropriate.

Finally, Applicants allege that each reference does not teach all the limitations of the instant claims; however, each reference was not relied upon alone. Rather, it's the combination of references that teach all the elements of Applicants' claims, with proper motivation and a reasonable expectation of success as outlined in the previous Office action, that render the instant claims obvious. Since Applicants' arguments regarding different sequences and functional limitations of the instant compounds are not persuasive as outlined above, and because Applicant has not provided any further arguments rebutting the instant rejection, the claims above stand rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James Douglas Schultz, PhD
February 6, 2003